

# Non-homogeneous random walks and subdiffusive transport of cells

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**Abstract.** This paper is concerned with a non-homogeneous in space and non-local in time random walk model for anomalous subdiffusive transport of cells. Starting with a Markov model involving a structured probability density function, we derive the non-local in time master equation and fractional equation for the probability of cell position. We show the structural instability of fractional subdiffusive equation with respect to the partial variations of anomalous exponent. We find the criteria under which the anomalous aggregation of cells takes place in the semi-infinite domain.

**Key words:** anomalous random walks, cell migration, aggregation

**AMS subject classification:**

## 1. Introduction

Random cell movement plays a very important role in embryonic morphogenesis, wound healing, cancer cells proliferation, and many other physiological and pathological processes [34]. The microscopic theory of the migration of cells and bacteria towards a favorable environment (chemotaxis) is based on random walk models [8, 19, 31, 32]. The “velocity-jump” models concern with self-propelled motion involving the runs and tumbles, while “space-jump” models deal with the cells making jumps in space. Much of the literature on the theoretical studies of cells motility has been concerned with Markov random walk models (see, for example, [4, 8]). However, the analysis of random movement of wild-type and mutated epithelial cells shows the anomalous dynamics of cell migration [7] (see also [27]). Over the past few years there have been several attempts to model non-Markovian anomalous cell transport involving subdiffusion and superdiffusion [7, 9, 10, 12, 13, 17]. In this paper we shall deal with a non-Markovian “space-jump” model

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that describes the non-homogeneous in space subdiffusive transport of cells.

First let us consider a Markov model for random cell movement along one-dimensional lattice such that all steps are of equal length 1. We define the probability

$$p(k, t) = \Pr \{X(t) = k\} \quad (1.1)$$

that the position of cell  $X(t)$  is at point  $k \in \mathbb{Z}$  at time  $t$ . We introduce at each point  $k$  the rate of jump to the left  $\mu(k)$  and the rate of jump to the right  $\lambda(k)$ . This random walk is called a generalized birth-death process [6]. The master equation for  $p(k, t)$  can be written as

$$\frac{\partial p(k, t)}{\partial t} = \lambda(k-1)p(k-1, t) + \mu(k+1)p(k+1, t) - (\lambda(k) + \mu(k))p(k, t). \quad (1.2)$$

This model corresponds to the case when intervals between jumps at point  $k$  are exponentially distributed with parameter  $\lambda(k) + \mu(k)$ . When the cell makes a jump from the position  $k$ , it jumps to the right with probability  $\lambda(k)/(\lambda(k) + \mu(k))$  and to the left with the probability  $\mu(k)/(\lambda(k) + \mu(k))$  [6].

The dependence of  $\mu(k)$  and  $\lambda(k)$  on space can be introduced in different ways depending on how cells sense the surrounding environment. For the local chemotaxis models, the rates  $\lambda(S(k))$  and  $\mu(S(k))$  are the functions of the local concentration of the chemotactic substance  $S(k)$ . In the continuous limit, the master equation (1.2) can be reduced to the classical advection-diffusion equation in which the cell flux involves the standard diffusion term and the advection term due to chemotaxis. Note that there exist several non-local and barrier models that are different in terms of the dependence of rate functions on the chemotactic substance. For example, the rates  $\mu(k)$  and  $\lambda(k)$  can depend on the concentration of the chemotactic substance at neighbouring positions  $k-1$  and  $k+1$  (see the details in [32, 4]). If we consider only positive values of  $k$ , we need to implement boundary conditions at the point  $k=1$ . Here we assume that if cell hits the wall on the boundary, it is reflected with the probability  $1 - \chi$  and absorbed by wall with the probability  $\chi$ . Then one can write  $p(1, t + \Delta t) = (1 - \lambda(1)\Delta t - \mu(1)\Delta t)p(1, t) + \mu(1)(1 - \chi)p(1, t)\Delta t + \mu(2)p(2, t)\Delta t + o(\Delta t)$ . In the limit  $\Delta t \rightarrow 0$  we obtain

$$\frac{\partial p(1, t)}{\partial t} = -\chi\mu(1)p(1, t) + \mu(2)p(2, t) - \lambda(1)p(1, t), \quad (1.3)$$

where  $0 \leq \chi \leq 1$ .

Non-uniform stationary solution of master equation (1.2) can be interpreted as cell aggregation phenomenon [32]. In particular, if there is no absorption on the boundary ( $\chi = 0$ ), the stationary solution  $p_{st}(k)$  can be easily found from (1.2) and (1.3). We obtain

$$p_{st}(k) = p_{st}(1) \prod_{I=1}^{k-1} \frac{\lambda(I)}{\mu(I+1)}, \quad k > 1, \quad (1.4)$$

where

$$p_{st}(1) = \left( 1 + \sum_{k=2}^{\infty} \prod_{I=1}^{k-1} \frac{\lambda(I)}{\mu(I+1)} \right)^{-1}$$

provided the series is convergent.

It is tempting to generalize the master equation (1.2) for the anomalous case by replacing the time derivative with the Caputo derivative [2, 24]

$$\frac{\partial^\nu p(k, t)}{\partial t^\nu} = \frac{1}{\Gamma(1-\nu)} \int_0^t \frac{\partial p(k, u)}{\partial u} \frac{du}{(t-u)^{1-\nu}} \quad (1.5)$$

as it is done in [33] for a fractional linear birth–death process. Here  $\nu$  is the anomalous exponent:  $0 < \nu < 1$ . Although this generalization is very attractive from a mathematical point of view, it is not appropriate for a non-homogeneous medium for which the exponent  $\nu$  depends on  $k$ . The non-homogeneous fractional equation for  $p(k, t)$  can be written as

$$\frac{\partial p(k, t)}{\partial t} = a(k-1) \mathcal{D}_t^{1-\nu(k-1)} p(k-1, t) + b(k+1) \mathcal{D}_t^{1-\nu(k+1)} p(k+1, t) - (a(k) + b(k)) \mathcal{D}_t^{1-\nu(k)} p(k, t), \quad (1.6)$$

where  $\mathcal{D}_t^{1-\nu(k)}$  is the Riemann-Liouville fractional derivative with varying order

$$\mathcal{D}_t^{1-\nu(k)} p(k, t) = \frac{1}{\Gamma(\nu(k))} \frac{\partial}{\partial t} \int_0^t \frac{p(k, u) du}{(t-u)^{1-\nu(k)}}. \quad (1.7)$$

Here  $\nu(k)$  is the anomalous exponent corresponding to the site  $k$  and the anomalous rate coefficients  $a(k)$  and  $b(k)$  have to be determined (see (3.10)). The crucial point here is that the anomalous exponent  $\nu(k)$  depends on the site  $k$ . The fractional equation (1.6) cannot be rewritten in terms of Caputo derivative (1.5). It turns out that even small non-homogeneous variations of the exponent  $\nu$  lead to a drastic change of  $p(k, t)$  in the limit  $t \rightarrow \infty$  [14]. It means that the subdiffusive fractional equations with constant anomalous exponent  $\nu$  are *not structurally stable*. If, for example, the point  $k = M$  has the property that  $\nu(M) < \nu(k)$  for all  $k \neq M$  and  $\chi = 0$ , one can find that

$$p(k, t) \rightarrow 0, \quad p(M, t) \rightarrow 1, \quad 1 \leq k \leq N \quad (1.8)$$

as  $t \rightarrow \infty$ . This result has been interpreted as anomalous aggregation of cells at the point  $k = M$  [12]. In this paper we shall find the conditions for anomalous aggregation for the semi-infinite interval  $1 \leq k < \infty$ . It should also be noted that non-homogeneous variations of the exponent  $\nu$  destroy the Gibbs-Boltzmann distribution as a long time limit of the fractional Fokker-Planck equation [14].

Another extension of traditional Markov random walks models is non-Markovian theory of anomalous transport with reaction dynamics [11, 28, 30, 35, 36, 20]. In particular, this theory has been used for the analysis of the proliferation and migration dichotomy of cancer cells [9, 10, 13]. In this paper we consider the inhibition of cell growth by anticancer therapeutic agents. To model this inhibition we introduce the random death process with non-uniform death rate parameter. We assume that during time interval  $(t, t + \Delta t)$  at point  $k$  each cell has a chance  $\theta(k)\Delta t + o(\Delta t)$  of dying, where  $\theta(k)$  is the death rate. It is easy to take into account this process for Markov models. We just add the term  $-\theta(k)p(k, t)$  to the right hand side of the master equation (1.2). On the contrary, the anomalous master equation involves a non-trivial combination of transport and death

kinetic terms because of memory effects [18, 28, 1]. In this paper we shall derive the following fractional equation

$$\begin{aligned} \frac{\partial p(k, t)}{\partial t} = & a(k-1)e^{-\theta(k-1)t} \mathcal{D}_t^{1-\nu(k-1)} [p(k-1, t)e^{\theta(k-1)t}] \\ & + b(k+1)e^{-\theta(k+1)t} \mathcal{D}_t^{1-\nu(k+1)} [p(k+1, t)e^{\theta(k+1)t}] \\ & - (a(k) + b(k)) e^{-\theta(k)t} \mathcal{D}_t^{1-\nu(k)} [p(k, t)e^{\theta(k)t}] - \theta(k)p(k, t). \end{aligned} \quad (1.9)$$

Instead of the probability  $p(k, t)$  for an individual cell one can consider the mean density of cells  $\rho(x, t)$  as a function of space  $x$  and time  $t$ . Then the master equation (1.2) for the density  $\rho(x, t)$  can be written as

$$\frac{\partial \rho(x, t)}{\partial t} = \lambda(x-l)\rho(x-l, t) + \mu(x+l)\rho(x+l, t) - (\lambda(x) + \mu(x))\rho(x, t) - \theta(x)\rho(x, t), \quad (1.10)$$

where  $l$  is the jump size,  $\theta(x)$  is the death rate. The advantage of this equation is that one can easily take into account various non-linear effects by assuming the dependence of the rate functions  $\lambda(x)$ ,  $\mu(x)$  and  $\theta(x)$  on the average density  $\rho(x, t)$ .

In the anomalous subdiffusive case, the master equation for mean field  $\rho(x, t)$  becomes non-local in time. It can be written as a mass balance equation

$$\frac{\partial \rho(x, t)}{\partial t} = -I(x, t) + I(x-l, t) - \theta(x)\rho(x, t), \quad (1.11)$$

where  $I(x, t)$  is the total flow of cells from the point  $x$  to  $x+l$

$$I(x, t) = a(x)e^{-\theta(x)t} \mathcal{D}_t^{1-\nu(x)} [e^{\theta(x)t} \rho(x, t)] - b(x+l)e^{-\theta(x+l)t} \mathcal{D}_t^{1-\nu(x+l)} [e^{\theta(x+l)t} \rho(x+l, t)] \quad (1.12)$$

and  $I(x-l, t)$  is the total flow of cells from the point  $x-l$  to  $x$

$$I(x-l, t) = a(x-l)e^{-\theta(x-l)t} \mathcal{D}_t^{1-\nu(x-l)} [e^{\theta(x-l)t} \rho(x-l, t)] - b(x)e^{-\theta(x)t} \mathcal{D}_t^{1-\nu(x)} [e^{\theta(x)t} \rho(x, t)]. \quad (1.13)$$

Here  $a(x)$  and  $b(x)$  are the anomalous rate functions (see (3.10)). One can see that the flow of cells  $I(x, t)$  depends on the death rate  $\theta(x)$ . It means that in the anomalous case one cannot separate the transport of cells from the death process [18]. This phenomenon does not exist in the Markovian case. For the Markov model (1.10) the flux  $I(x, t)$  is independent from  $\theta(x)$ :

$$I(x, t) = \lambda(x)\rho(x, t) - \mu(x+l)\rho(x+l, t).$$

When the density  $\rho(x, t)$  is conserved ( $\theta = 0$ ), the master equation (1.11) can be approximated by the fractional Fokker-Planck equation [2, 25, 26]

$$\frac{\partial \rho(x, t)}{\partial t} = \frac{\partial}{\partial x} \left[ l(a(x) - b(x)) \mathcal{D}_t^{1-\nu(x)} \rho(x, t) \right] + \frac{\partial^2}{\partial x^2} \left[ \frac{l^2}{2} (a(x) + b(x)) \mathcal{D}_t^{1-\nu(x)} \rho(x, t) \right]. \quad (1.14)$$

This is an example of the fractional equation with varying anomalous exponent [5]. Note that  $a(x) - b(x) \sim l$  as  $l \rightarrow 0$  (see (3.16) and (3.18)). The purpose of the next section is to set up a non-Markovian discrete-space random walk model describing cell motility involving memory effects, the death process and subdiffusive transport.

## 2. Non-Markovian discrete-space random walk model

### 2.1. Random cell motility

There exist numerous mechanisms that facilitate random cell movement [34]. In this paper we adopt the following random model of cell motility. When the cell makes a jump to position  $k$ , the time the cell spends here before it makes a jump to point  $k - 1$  or  $k + 1$  is random. It is called the residence time or waiting (holding) time. We define the residence time at position  $k$  as

$$T_k = \min(T_k^\mu, T_k^\lambda), \quad (2.1)$$

where  $T_k^\mu$  and  $T_k^\lambda$  are the independent random times of jump to the left and right respectively. The idea here is that there exist internal cellular signals involving two "hidden" independent random alarm clocks. If one of the clocks goes off first, say  $T_k^\lambda < T_k^\mu$ , the cell moves to the right to the point  $k + 1$ . The other clock "tells" the cell to move left to the point  $k - 1$  if it goes off first ( $T_k^\mu < T_k^\lambda$ ). Note that migration of cells is a highly complicated dynamic process which is regulated by both intercellular signals and the surrounding environment. Since we do not know the exact mechanism of cell motility we use a stochastic approach involving two random times  $T_k^\mu$  and  $T_k^\lambda$  for jumping to the left and right. Note that if the random times  $T_k^\mu$  and  $T_k^\lambda$  are exponentially distributed with the rates  $\mu(k)$  and  $\lambda(k)$  respectively, we have a classical Markov model with the master equation (1.2). If the random variables  $T_k^\mu$  and  $T_k^\lambda$  are not exponentially distributed, the standard Markov approach does not work. In this section we consider the non-Markovian case when  $T_k^\mu$  and  $T_k^\lambda$  are independent positive random variables with general survival functions

$$\Psi_\mu(k, \tau) = \Pr\{T_k^\mu > \tau\}, \quad \Psi_\lambda(k, \tau) = \Pr\{T_k^\lambda > \tau\}. \quad (2.2)$$

The Markov model (1.2) corresponds to the following choice

$$\Psi_\mu(k, \tau) = e^{-\mu(k)\tau}, \quad \Psi_\lambda(k, \tau) = e^{-\lambda(k)\tau}. \quad (2.3)$$

It is convenient to introduce the rate of escape (hazard function)  $\gamma(k, \tau)$  from the point  $k$  as

$$\gamma(k, \tau) = \lim_{h \rightarrow 0} \frac{\Pr\{\tau < T_k < \tau + h \mid T_k > \tau\}}{h}. \quad (2.4)$$

If we denote the survival function at the point  $k$  as

$$\Psi(k, \tau) = \Pr\{T_k > \tau\}$$

and the residence time probability density function as

$$\psi(k, \tau) = -\frac{\partial \Psi(k, \tau)}{\partial \tau},$$

then [6]

$$\gamma(k, \tau) = \frac{\psi(k, \tau)}{\Psi(k, \tau)}. \quad (2.5)$$

Now we determine this rate function in terms of statistical characteristics of random residence times  $T_k^\mu$  and  $T_k^\lambda$ . It follows from the definition of the residence time  $T_k$  at position  $k$  (2.1) that the survival function  $\Psi(k, \tau)$  can be written as a product

$$\Psi(k, \tau) = \Psi_\lambda(k, \tau)\Psi_\mu(k, \tau),$$

where  $\Psi_\lambda(k, \tau)$  and  $\Psi_\mu(k, \tau)$  are defined by (2.2). Differentiation of this equation with respect to  $\tau$  gives

$$\psi(k, \tau) = \psi_\lambda(k, \tau) + \psi_\mu(k, \tau), \quad (2.6)$$

where the transition probability density functions  $\psi_\lambda(k, \tau)$  and  $\psi_\mu(k, \tau)$  are defined as

$$\psi_\lambda(k, \tau) = -\frac{\partial \Psi_\lambda(k, \tau)}{\partial \tau} \Psi_\mu(k, \tau), \quad \psi_\mu(k, \tau) = -\frac{\partial \Psi_\mu(k, \tau)}{\partial \tau} \Psi_\lambda(k, \tau). \quad (2.7)$$

The formula (2.6) is the particular case of the general expression for the residence time PDF in terms of the transition probability densities (see formula (5) in the classical paper by van Kampen [22]). These transition PDF's have a clear probabilistic meaning. For example,  $\psi_\mu(k, \tau)\Delta\tau$  is the probability that the cell's jump to the left occurs in the time interval  $(\tau, \tau + \Delta\tau)$  since the cell arrived at point  $k$ . If we divide both sides of (2.6) by the survival function  $\Psi(k, \tau)$  and use the formula (2.5), we obtain

$$\gamma(k, \tau) = \lambda(k, \tau) + \mu(k, \tau), \quad (2.8)$$

where the rate of jump to the right  $\lambda(k, \tau)$  and the rate of jump to the left  $\mu(k, \tau)$  are defined as

$$\lambda(k, \tau) = \frac{\psi_\lambda(k, \tau)}{\Psi(k, \tau)}, \quad \mu(k, \tau) = \frac{\psi_\mu(k, \tau)}{\Psi(k, \tau)}. \quad (2.9)$$

Note that the transition rates  $\lambda(k, \tau)$  and  $\mu(k, \tau)$  can be introduced from the very beginning as it is done in [22]. By using (2.5) and (2.8), we write the survival function  $\Psi(k, \tau)$  as

$$\Psi(k, \tau) = e^{-\int_0^\tau \lambda(k, \tau) d\tau - \int_0^\tau \mu(k, \tau) d\tau}. \quad (2.10)$$

The residence time probability density function  $\psi(k, \tau)$  takes the form

$$\psi(k, \tau) = (\lambda(k, \tau) + \mu(k, \tau))e^{-\int_0^\tau \lambda(k, \tau) d\tau - \int_0^\tau \mu(k, \tau) d\tau}.$$

For the Markov case for which  $\lambda(k)$  and  $\mu(k)$  are independent of the residence time variable  $\tau$ , we obtain from (2.10) the standard exponential survival function

$$\Psi(k, \tau) = e^{-\lambda(k)\tau - \mu(k)\tau}$$

corresponding to the Markov master equation (1.2).

## 2.2. Structured probability density function

If the residence time probability density function  $\psi$  is not exponential, the random walk is non-Markovian. The standard method to deal with non-Markovian stochastic processes is to add auxiliary variables to the definition of the random walk to make the process Markovian [6]. Here we introduce the structured probability density function  $\xi(k, t, \tau)$  involving residence time  $\tau$  as auxiliary variable. The structural density gives the probability that the cell position  $X(t)$  at time  $t$  is at the point  $k$  and its residence time  $T_k$  at point  $k$  is in the interval  $(\tau, \tau + d\tau)$ . This is a standard way to deal with non-Markovian random walks [6, 28]. Suppose that cells die at random at rate  $\theta(k)$  that depends on  $k$ . The density  $\xi(k, t, \tau)$  obeys the balance equation

$$\frac{\partial \xi}{\partial t} + \frac{\partial \xi}{\partial \tau} = -\lambda(k, \tau)\xi - \mu(k, \tau)\xi - \theta(k)\xi. \quad (2.11)$$

We consider only the case when the residence time of random walker at  $t = 0$  is equal to zero, so the initial condition is

$$\xi(k, 0, \tau) = p_0(k)\delta(\tau), \quad (2.12)$$

where  $p_0(k) = \Pr\{X(0) = k\}$ . The boundary condition in terms of residence time variable ( $\tau = 0$ ) can be written as [6]

$$\xi(k, t, 0) = \int_0^t \lambda(k-1, \tau)\xi(k-1, t, \tau)d\tau + \int_0^t \mu(k+1, \tau)\xi(k+1, t, \tau)d\tau. \quad (2.13)$$

In what follows we consider only positive values of  $k$ . In which case, we have to specify the boundary condition for  $k = 1$ . We write

$$\xi(1, t, 0) = (1 - \chi) \int_0^t \mu(1, \tau)\xi(1, t, \tau)d\tau + \int_0^t \mu(2, \tau)\xi(2, t, \tau)d\tau. \quad (2.14)$$

This equation tells us that when cells escape from the point  $k = 1$  and move to the left with the rate  $\mu(1, \tau)$ , they are adsorbed by the wall with probability  $\chi$ , and reflected back to the position  $k = 1$  with the probability  $1 - \chi$ . Note that this boundary condition can be written in many different ways, for example, the cells can be reflected to state  $k = 2$ . One can also introduce a residence time PDF for a wall such that the reflection is not instantaneous.

We solve (2.11) by the method of characteristics

$$\xi(k, t, \tau) = \xi(k, t - \tau, 0)e^{-\int_0^\tau \lambda(k, \tau)d\tau - \int_0^\tau \mu(k, \tau)d\tau - \theta(k)\tau}, \quad \tau < t, \quad k \geq 1. \quad (2.15)$$

The structural density  $\xi$  can be rewritten in terms of the survival function  $\Psi(k, \tau)$  (2.10) and the integral arrival rate

$$j(k, t) = \xi(k, t, 0)$$

as

$$\xi(k, t, \tau) = j(k, t - \tau)\Psi(k, \tau)e^{-\theta(k)\tau}, \quad \tau < t, \quad k \geq 1. \quad (2.16)$$



Our purpose now is to derive the master equation for the probability  $p(k, t) = \Pr \{X(t) = k\}$  :

$$p(k, t) = \int_0^t \xi(k, t, \tau) d\tau, \quad k \geq 1. \quad (2.17)$$

Let us introduce the integral escape rate to the right  $i_\lambda(k, t)$  and the integral escape rate to the left  $i_\mu(k, t)$  as

$$i_\lambda(k, t) = \int_0^t \lambda(k, \tau) \xi(k, t, \tau) d\tau, \quad i_\mu(k, t) = \int_0^t \mu(k, \tau) \xi(k, t, \tau) d\tau. \quad (2.18)$$

Then the boundary conditions (2.13) and (2.14) can be written in a very simple form:

$$j(k, t) = i_\lambda(k-1, t) + i_\mu(k+1, t), \quad k > 1 \quad (2.19)$$

and

$$j(1, t) = (1 - \chi) i_\mu(1, t) + i_\mu(2, t). \quad (2.20)$$

It follows from (2.9), (2.12), (2.16) and (2.18) that

$$i_\lambda(k, t) = \int_0^t \psi_\lambda(k, \tau) j(k, t - \tau) e^{-\theta(k)\tau} d\tau + \psi_\lambda(k, t) p_0(k) e^{-\theta(k)t}, \quad (2.21)$$

$$i_\mu(k, t) = \int_0^t \psi_\mu(k, \tau) j(k, t - \tau) e^{-\theta(k)\tau} d\tau + \psi_\mu(k, t) p_0(k) e^{-\theta(k)t}. \quad (2.22)$$

Substitution of (2.12) and (2.16) to (2.17), gives

$$p(k, t) = \int_0^t \Psi(k, \tau) j(k, t - \tau) e^{-\theta(k)\tau} d\tau + \Psi(k, t) p_0(k) e^{-\theta(k)t}. \quad (2.23)$$

It is convenient to introduce the integral escape rate  $i(k, t)$  as the sum of the escape rate to the right  $i_\lambda(k, t)$  and the escape rate to the left  $i_\mu(k, t)$

$$i(k, t) = i_\lambda(k, t) + i_\mu(k, t). \quad (2.24)$$

The balance equation for  $p(k, t)$  can be written as

$$\frac{\partial p(k, t)}{\partial t} = -i(k, t) + j(k, t) - \theta(k)p(k, t), \quad k > 1. \quad (2.25)$$

To obtain a closed equation for  $p(k, t)$  we need to express  $i(k, t)$  and  $j(k, t)$  in terms of  $p(k, t)$ . By applying the Laplace transform  $\hat{\psi}(k, s) = \int_0^\infty \psi(k, \tau) e^{-s\tau} d\tau$  to (2.21), (2.22) and (2.23), we obtain

$$\hat{i}_\lambda(k, s) = \hat{\psi}_\lambda(k, s + \theta(k)) [\hat{j}(k, s) + p_0(k)],$$

$$\hat{i}_\mu(k, s) = \hat{\psi}_\mu(k, s + \theta(k)) [\hat{j}(k, s) + p_0(k)]$$



and

$$\hat{p}(k, s) = \hat{\Psi}(k, s + \theta(k)) [\hat{j}(k, s) + p_0(k)].$$

In the Laplace space we have the following expressions for escape rates

$$\hat{i}_\lambda(k, s) = \frac{\hat{\psi}_\lambda(k, s + \theta(k))}{\hat{\Psi}(k, s + \theta(k))} \hat{p}(k, s), \quad \hat{i}_\mu(k, s) = \frac{\hat{\psi}_\mu(k, s + \theta(k))}{\hat{\Psi}(k, s + \theta(k))} \hat{p}(k, s). \quad (2.26)$$

Using inverse Laplace transform and shift theorem we find

$$\begin{aligned} i_\lambda(k, t) &= \int_0^t K_\lambda(k, t - \tau) e^{-\theta(k)(t-\tau)} p(k, \tau) d\tau, \\ i_\mu(k, t) &= \int_0^t K_\mu(k, t - \tau) e^{-\theta(k)(t-\tau)} p(k, \tau) d\tau, \end{aligned} \quad (2.27)$$

where  $K_\lambda(k, t)$  and  $K_\mu(k, t)$  are the memory kernels defined by Laplace transforms

$$\hat{K}_\lambda(k, s) = \frac{\hat{\psi}_\lambda(k, s)}{\hat{\Psi}(k, s)}, \quad \hat{K}_\mu(k, s) = \frac{\hat{\psi}_\mu(k, s)}{\hat{\Psi}(k, s)}. \quad (2.28)$$

It follows from (2.19), (2.24), (2.25) and (2.27) that the master equation for the probability  $p(k, t)$  is

$$\begin{aligned} \frac{\partial p(k, t)}{\partial t} &= \int_0^t K_\lambda(k-1, t-\tau) p(k-1, \tau) e^{-\theta(k-1)(t-\tau)} d\tau \\ &+ \int_0^t K_\mu(k+1, t-\tau) p(k+1, \tau) e^{-\theta(k+1)(t-\tau)} d\tau \\ &- \int_0^t [K_\lambda(k, t-\tau) + K_\mu(k, t-\tau)] p(k, \tau) e^{-\theta(k)(t-\tau)} d\tau - \theta(k) p(k, t) \end{aligned} \quad (2.29)$$

for  $k > 1$ . The balance equation for  $k = 1$  is

$$\frac{\partial p(1, t)}{\partial t} = -\chi i_\mu(1, t) - i_\lambda(1, t) + i_\mu(2, t) - \theta(1) p(1, t)$$

or

$$\begin{aligned} \frac{\partial p(1, t)}{\partial t} &= -\chi \int_0^t K_\mu(1, t-\tau) p(1, \tau) e^{-\theta(1)(t-\tau)} d\tau - \int_0^t K_\lambda(1, t-\tau) p(1, \tau) e^{-\theta(1)(t-\tau)} d\tau \\ &+ \int_0^t K_\mu(2, t-\tau) p(2, \tau) e^{-\theta(2)(t-\tau)} d\tau - \theta(1) p(1, t), \end{aligned} \quad (2.30)$$

where  $0 \leq \chi \leq 1$ . The master equation for  $p(k, t)$  can be rewritten in terms of the probability flux  $I(k, t)$  from the point  $k$  to  $k+1$

$$I(k, t) = \int_0^t K_\lambda(k, t-\tau) p(k, \tau) e^{-\theta(k)(t-\tau)} d\tau - \int_0^t K_\mu(k+1, t-\tau) p(k+1, \tau) e^{-\theta(k+1)(t-\tau)} d\tau \quad (2.31)$$

as

$$\frac{\partial p(k, t)}{\partial t} = -I(k, t) + I(k-1, t) - \theta(k)p(k, t). \quad (2.32)$$

In the next section we shall derive fractional master equation for  $p(k, t)$ .

### 3. Anomalous subdiffusion in heterogeneous media

We now turn to the anomalous subdiffusive case. We assume that the longer cell survives at point  $k$ , the smaller the transition probability from  $k$  becomes. It means that the transition rates  $\lambda(k, \tau)$  and  $\mu(k, \tau)$  are decreasing functions of residence time  $\tau$ . We assume that

$$\lambda(k, \tau) = \frac{\nu_\lambda(k)}{\tau_0(k) + \tau}, \quad \mu(k, \tau) = \frac{\nu_\mu(k)}{\tau_0(k) + \tau}, \quad (3.1)$$

where  $\tau_0(k)$  is a parameter with units of time. Both  $\nu_\lambda(k)$  and  $\nu_\mu(k)$  play a very important role in what follows. From (2.10) and (3.1) we find that the survival function has a power-law dependence

$$\Psi(k, \tau) = \left( \frac{\tau_0(k)}{\tau_0(k) + \tau} \right)^{\nu(k)},$$

where the exponent

$$\nu(k) = \nu_\lambda(k) + \nu_\mu(k) \quad (3.2)$$

depends on the state  $k$ . Residence time probability density function  $\psi(k, \tau) = -\partial\Psi(k, \tau)/\partial\tau$  has the Pareto form

$$\psi(k, \tau) = \frac{\nu(k) (\tau_0(k))^{\nu(k)}}{(\tau_0(k) + \tau)^{1+\nu(k)}}, \quad (3.3)$$

The anomalous subdiffusive case [2, 28] corresponds to

$$\nu(k) = \nu_\lambda(k) + \nu_\mu(k) < 1.$$

We can notice from (3.1) that the ratios  $\lambda(k, \tau)$  and  $\mu(k, \tau)$  to  $\lambda(k, \tau) + \mu(k, \tau)$  are independent of the residence time variable  $\tau$  that is

$$\frac{\lambda(k, \tau)}{\lambda(k, \tau) + \mu(k, \tau)} = \frac{\nu_\lambda(k)}{\nu_\lambda(k) + \nu_\mu(k)}, \quad \frac{\mu(k, \tau)}{\lambda(k, \tau) + \mu(k, \tau)} = \frac{\nu_\mu(k)}{\nu_\lambda(k) + \nu_\mu(k)}.$$

In this case it is convenient to introduce the probabilities of jumping to the right

$$p_\lambda(k) = \frac{\nu_\lambda(k)}{\nu_\lambda(k) + \nu_\mu(k)} \quad (3.4)$$

and to the left

$$p_\mu(k) = \frac{\nu_\mu(k)}{\nu_\lambda(k) + \nu_\mu(k)}. \quad (3.5)$$

Note that these jump probabilities are completely determined by the anomalous exponents  $\nu_\lambda(k)$  and  $\nu_\mu(k)$ . Note that in the standard CTRW theory, these jump probabilities are given independently [2, 28]. The corresponding transition PDF's  $\psi_\lambda(k, \tau) = \lambda(k, \tau)\Psi(k, \tau)$  and  $\psi_\mu(k, \tau) = \mu(k, \tau)\Psi(k, \tau)$  can be rewritten in terms of  $\psi(k, \tau)$

$$\psi_\lambda(k, \tau) = p_\lambda(k)\psi(k, \tau), \quad \psi_\mu(k, \tau) = p_\mu(k)\psi(k, \tau). \quad (3.6)$$

The asymptotic approximation for the Laplace transform of the waiting time density  $\psi(k, \tau)$  of the Pareto form (3.3) can be found from the Tauberian theorem [15]

$$\hat{\psi}(k, s) \simeq 1 - g(k)s^{\nu(k)}, \quad s \rightarrow 0$$

with

$$g(k) = \Gamma(1 - \nu(k)) (\tau_0(k))^{\nu(k)}. \quad (3.7)$$

We obtain from (2.28) and (3.6) the Laplace transforms of the memory kernels

$$\hat{K}_\lambda(k, s) \simeq \frac{p_\lambda(k)s^{1-\nu(k)}}{g(k)}, \quad \hat{K}_\mu(k, s) \simeq \frac{p_\mu(k)s^{1-\nu(k)}}{g(k)}, \quad s \rightarrow 0. \quad (3.8)$$

Therefore, the integral escape rates to the right  $i_\lambda(k, t)$  and to the left  $i_\mu(k, t)$  in the subdiffusive case are

$$\begin{aligned} i_\lambda(k, t) &= a(k)e^{-\theta(k)t} \mathcal{D}_t^{1-\nu(k)} [p(k, t)e^{\theta(k)t}], \\ i_\mu(k, t) &= b(k)e^{-\theta(k)t} \mathcal{D}_t^{1-\nu(k)} [p(k, t)e^{\theta(k)t}]. \end{aligned} \quad (3.9)$$

Here  $\mathcal{D}_t^{1-\nu(k)}$  is the Riemann-Liouville fractional derivative with varying order defined by (1.7). The anomalous rate functions  $a(k)$  and  $b(k)$  are

$$a(k) = \frac{p_\lambda(k)}{g(k)} = \frac{\nu_\lambda(k)}{\nu(k)\Gamma(1 - \nu(k)) (\tau_0(k))^{\nu(k)}}, \quad (3.10)$$

$$b(k) = \frac{p_\mu(k)}{g(k)} = \frac{\nu_\mu(k)}{\nu(k)\Gamma(1 - \nu(k)) (\tau_0(k))^{\nu(k)}} \quad (3.11)$$

with the anomalous exponent  $\nu(k)$  defined in (3.2). The master equation (2.29) takes the form of non-homogeneous fractional equation

$$\begin{aligned} \frac{\partial p(k, t)}{\partial t} &= a(k-1)e^{-\theta(k-1)t} \mathcal{D}_t^{1-\nu(k-1)} [p(k-1, t)e^{\theta(k-1)t}] \\ &\quad + b(k+1)e^{-\theta(k+1)t} p(k+1, t) \mathcal{D}_t^{1-\nu(k+1)} [p(k+1, t)e^{\theta(k+1)t}] \\ &\quad - (a(k) + b(k)) e^{-\theta(k)t} \mathcal{D}_t^{1-\nu(k)} [p(k, t)e^{\theta(k)t}] - \theta(k)p(k, t) \end{aligned} \quad (3.12)$$

for  $k > 1$ .

For  $k = 1$  with  $\theta(k) = \chi = 0$ , we obtain

$$\frac{\partial p(1, t)}{\partial t} = b(2)\mathcal{D}_t^{1-\nu(2)}p(2, t) - a(1)\mathcal{D}_t^{1-\nu(1)}p(1, t). \quad (3.13)$$

The fractional probability flux  $I_\nu(k, t)$  from the point  $k$  to  $k + 1$  is

$$I_\nu = a(k)e^{-\theta(k)t}\mathcal{D}_t^{1-\nu(k)}[p(k, t)e^{\theta(k)t}] - b(k+1)e^{-\theta(k+1)t}p(k+1)\mathcal{D}_t^{1-\nu(k+1)}[p(k+1, t)e^{\theta(k+1)t}]. \quad (3.14)$$

The equation (3.12) can be rewritten in terms of the probability flux  $I_\nu(k, t)$  as

$$\frac{\partial p(k, t)}{\partial t} = -I_\nu(k, t) + I_\nu(k-1, t) - \theta(k)p(k, t). \quad (3.15)$$

Note that in the continuous case ( $x$  instead of  $k$ ), the anomalous advection  $l(a(x) - b(x))$  in the fractional Fokker-Planck equation (1.14) is proportional to the difference in the anomalous exponents  $\nu_\lambda(x)$  and  $\nu_\mu(x)$ , since

$$a(x) - b(x) = \frac{p_\lambda(x) - p_\mu(x)}{g(x)} = \frac{\nu_\lambda(x) - \nu_\mu(x)}{\nu(x)\Gamma(1 - \nu(x))(\tau_0(x))^{\nu(x)}}. \quad (3.16)$$

The difference  $\nu_\lambda(x) - \nu_\mu(x)$  can be approximated in the different ways. For example, in the case of chemotaxis this difference is proportional to the gradient of the local concentration of the chemotactic substance  $S(x)$ . Let us show this. We consider the standard non-local model for which the jump probabilities  $p_\lambda(k)$  and  $p_\mu(k)$  depends on the chemotactic substance  $S(k)$  as follows [32, 4]

$$\begin{aligned} p_\lambda(k) &= Ae^{\beta(S(k+1)-S(k))}, \\ p_\mu(k) &= Ae^{\beta(S(k-1)-S(k))}, \end{aligned} \quad (3.17)$$

where the parameter  $A$  is determined from  $p_\lambda(k) + p_\mu(k) = 1$ . Then [17]

$$p_\lambda(k) - p_\mu(k) = \frac{e^{\beta S(k+1)} - e^{\beta S(k-1)}}{e^{\beta S(k+1)} + e^{\beta S(k-1)}}.$$

In the continuous case

$$p_\lambda(x) - p_\mu(x) = \frac{e^{\beta S(x+l)} - e^{\beta S(x-l)}}{e^{\beta S(x+l)} + e^{\beta S(x-l)}}.$$

In the limit  $l \rightarrow 0$ , we obtain the standard chemotaxis model

$$p_\lambda(x) - p_\mu(x) = \beta l \frac{\partial S}{\partial x} + o(l) \quad (3.18)$$

for which the chemotaxis equation takes the form

$$\frac{\partial \rho(x, t)}{\partial t} = \frac{\partial}{\partial x} \left[ \frac{l^2 \beta}{g(x)} \frac{\partial S}{\partial x} \mathcal{D}_t^{1-\nu(x)} \rho(x, t) \right] + \frac{\partial^2}{\partial x^2} \left[ \frac{l^2}{2g(x)} \mathcal{D}_t^{1-\nu(x)} \rho(x, t) \right]. \quad (3.19)$$

In the next section we will be concerned with the asymptotic behavior of  $p(k, t)$  as  $t \rightarrow \infty$  for  $\theta(k) = 0$ .

## 4. Structural instability and anomalous aggregation

It has recently been shown that the subdiffusive fractional equations with constant anomalous exponent  $\nu$  in a bounded domain  $[0, L]$  are not structurally stable with respect to the non-homogeneous variations of parameter  $\nu$  [14]. It turns out that the spatial variations of the anomalous exponent lead to a drastic change in asymptotic behavior of  $p(k, t)$  for large  $t$ . The purpose of this section is to find the conditions of this structural instability in semi-infinite domain  $1 \leq k < \infty$ . We consider the case when  $\theta(k) = \chi = 0$  for which the total probability is conserved

$$\sum_{k=1}^{\infty} p(k, t) = 1 \quad (4.1)$$

and the fractional probability flux  $I_{\nu}(k, t)$  from the point  $k$  to  $k + 1$  is

$$I_{\nu}(k, t) = a(k)\mathcal{D}_t^{1-\nu(k)}p(k, t) - b(k+1)p(k+1)\mathcal{D}_t^{1-\nu(k+1)}p(k+1, t). \quad (4.2)$$

For simplicity we assume that the initial conditions are  $p_0(1) = 1$  and  $p_0(k) = 0$  for  $k \neq 1$ . Taking the Laplace transform of (1.6) and (4.1) we obtain

$$\begin{aligned} s\hat{p}(k, s) &= a(k-1)s^{1-\nu(k-1)}\hat{p}(k-1, s) + b(k+1)s^{1-\nu(k+1)}\hat{p}(k+1, s) \\ &\quad - (a(k) + b(k))s^{1-\nu(k)}\hat{p}(k, s) \end{aligned} \quad (4.3)$$

and

$$\sum_{k=1}^{\infty} s\hat{p}(k, s) = 1. \quad (4.4)$$

Since there is no flux of cells outside the left border, we have for  $k = 1$

$$s\hat{p}(1, s) - 1 = b(2)s^{1-\nu(2)}\hat{p}(2, s) - a(1)s^{1-\nu(1)}\hat{p}(1, s). \quad (4.5)$$

In the limit  $s \rightarrow 0$ , one can obtain from (4.5) simple formula expressing  $\hat{p}(2, s)$  in terms of  $\hat{p}(1, s)$

$$\hat{p}(2, s) \simeq \frac{a(1)s^{\nu(2)-\nu(1)}}{b(2)}\hat{p}(1, s), \quad s \rightarrow 0.$$

In general, we find from (4.3) and (4.5)  $\hat{p}(k, s)$  in terms of  $\hat{p}(k-1, s)$

$$\hat{p}(k, s) \simeq \frac{a(k-1)s^{\nu(k)-\nu(k-1)}}{b(k)}\hat{p}(k-1, s), \quad k > 1, \quad s \rightarrow 0. \quad (4.6)$$

This formula has very simple probabilistic meaning: the flux  $I_{\nu}(k-1, t) \rightarrow 0$  as  $t \rightarrow \infty$ . If we take the Laplace transform of  $I_{\nu}(k-1, t)$  from (4.2), we obtain

$$\hat{I}_{\nu}(k-1, s) = a(k-1)s^{1-\nu(k-1)}\hat{p}(k-1, s) - b(k)p(k)s^{1-\nu(k)}\hat{p}(k, s). \quad (4.7)$$

It follows from (4.6) that  $\hat{I}_{\nu}(k, s) \simeq 0$  as  $s \rightarrow 0$ .

#### 4.1. Stationary solution to fractional equation with constant anomalous exponent

Let us assume that the anomalous exponent  $\nu(k)$  is independent of the position  $k$  that is  $\nu = \text{const.}$  Let us find stationary solution to the fractional master equation (1.6)

$$p_{st}(k) = \lim_{t \rightarrow \infty} p(k, t) = \lim_{s \rightarrow 0} s \hat{p}(k, s). \quad (4.8)$$

It follows from (4.6) that

$$\hat{p}(k, s) \simeq \frac{a(k-1)}{b(k)} \hat{p}(k-1, s), \quad k > 1, \quad s \rightarrow 0.$$

or

$$\hat{p}(k, s) \simeq \prod_{j=1}^{k-1} \frac{a(j)}{b(j+1)} \hat{p}(1, s), \quad k > 1, \quad s \rightarrow 0. \quad (4.9)$$

Using the normalization condition (4.4) and (4.8), we obtain the stationary solution of the equation (1.6)

$$p_{st}(k) = p_{st}(1) \prod_{j=1}^{k-1} \frac{a(j)}{b(j+1)}, \quad k > 1, \quad (4.10)$$

where

$$p_{st}(1) = \left( 1 + \sum_{k=2}^{\infty} \prod_{j=1}^{k-1} \frac{a(j)}{b(j+1)} \right)^{-1}.$$

If the sum

$$\sum_{k=2}^{\infty} \prod_{j=1}^{k-1} \frac{a(j)}{b(j+1)}$$

is divergent, the stationary solution does not exist. In particular, if we assume that the anomalous rate functions  $a$  and  $b$  are equal, that is,  $a(k) = b(k+1)$ , then for a finite domain with  $k = 1, 2, \dots, N$ , we obtain uniform distribution  $p_{st}(k) = 1/N$  for every  $k$ . The stationary solution (4.10) is very similar to (1.4) corresponding to the Markov birth-death model. However, this similarity is very deceptive, because (4.10) is not structurally stable with respect to the non-homogeneous variations of parameter  $\nu$ . The aim of next subsection is to show this structural instability.

#### 4.2. Anomalous aggregation.

Now we consider non-homogeneous case for which the anomalous exponent depends on  $k$ . We assume that the point  $k = M$  has the property that  $\nu(M) < \nu(k)$  for all  $k \neq M$ . Our purpose now is to find the conditions under which

$$\lim_{t \rightarrow \infty} p(M, t) = 1, \quad \lim_{t \rightarrow \infty} p(k, t) = 0, \quad k \neq M. \quad (4.11)$$

It means that the total probability concentrates just at one point  $k = M$ . This phenomenon is called an anomalous aggregation [12]. This asymptotic behavior of cells was observed in experiments on phagotrophic protists when “cells become immobile in attractive patches, which will then eventually trap all cells” [16]. In the Laplace space, (4.11) takes the form

$$\lim_{s \rightarrow 0} s\hat{p}(M, s) = 1, \quad \lim_{s \rightarrow 0} s\hat{p}(k, s) = 0, \quad k \neq M.$$

We can rewrite the normalization condition (4.4) as

$$s\hat{p}(M, s) + \sum_{k=1}^{M-1} s\hat{p}(M-k, s) + \sum_{k=1}^{\infty} s\hat{p}(M+k, s) = 1. \quad (4.12)$$

By using (4.6), we express  $\hat{p}(M+k, s)$  in terms of  $\hat{p}(M, s)$  as follows

$$\hat{p}(M+k, s) \simeq \hat{p}(M, s) \prod_{j=1}^k \frac{a(M+j-1)}{b(M+j)} s^{\nu(M+k)-\nu(M)}, \quad k \geq 1, \quad s \rightarrow 0. \quad (4.13)$$

Now we write the formula for  $\hat{p}(M-k, s)$  in terms of  $\hat{p}(M, s)$

$$\hat{p}(M-k, s) \simeq \hat{p}(M, s) s^{\nu(M-k)-\nu(M)} \prod_{j=1}^k \frac{b(M-j+1)}{a(M-j)}, \quad k = 1, \dots, M-1, \quad s \rightarrow 0. \quad (4.14)$$

Now we substitute (4.13) and (4.14) into (4.12) and use  $s\hat{p}(M, s)$  as a common factor

$$s\hat{p}(M, s) \left( 1 + \sum_{k=1}^{M-1} s^{\nu(M-k)-\nu(M)} \prod_{j=1}^k \frac{b(M-j+1)}{a(M-j)} + \sum_{k=1}^{\infty} s^{\nu(M+k)-\nu(M)} \prod_{j=1}^k \frac{a(M+j-1)}{b(M+j)} \right) \simeq 1.$$

Since  $\nu(M) < \nu(k)$  for any  $k \neq M$ , we have  $s^{\nu(M+k)-\nu(M)} \rightarrow 0$  and  $s^{\nu(M-k)-\nu(M)} \rightarrow 0$  as  $s \rightarrow 0$ . We conclude that if

$$\sum_{k=1}^{\infty} s^{\nu(M+k)-\nu(M)} \prod_{j=1}^k \frac{a(M+j-1)}{b(M+j)} \rightarrow 0$$

as  $s \rightarrow 0$ , then  $s\hat{p}(M, s) \rightarrow 1$ , while  $s\hat{p}(k, s) \rightarrow 0$ . It means that in the limit  $t \rightarrow \infty$ , we obtain (4.11). If instead of probability  $p(k, t)$  we consider the mean density of cells  $\rho(x, t)$ , the formula (4.11) can be rewritten as  $\rho(x, t) \rightarrow \delta(x - x_{\min})$  as  $t \rightarrow \infty$ , where  $x_{\min}$  is the point on the interval  $[0, \infty)$  at which  $\nu(x)$  takes its minimum value. Note that this result was obtained for a symmetrical random walk in the context of chemotaxis and anomalous aggregation [12].

## 5. Conclusions.

We have studied a non-homogeneous in space and non-local in time random walk model describing anomalous subdiffusive transport of cells. Using a Markov model with structured probability



density function, we have derived non-local in time and fractional master equations for the probability of cell position. The advantage of our probabilistic approach is that it allows us to take into account the death process within the general non-Markovian random walk. The main feature of our fractional model is that the transition probabilities for jumping on the left and right depend inversely on the residence time variable. This dependence induces power-law residence time distribution and ultimately the anomalous subdiffusion of cells. It has recently been shown that the subdiffusive fractional equations with constant anomalous exponent are not structurally stable in a bounded domain with respect to the non-homogeneous variations. In this paper we have extended and complemented our previous results for infinite domain and found exact conditions under which the structural instability takes place. Our model can be generalized in many ways, e.g., by modelling the residence time by internal chemical reactions via a stochastic or ordinary differential equations instead of simple equation for the residence time  $d\tau/dt = 1$ . It would be interesting to take into account the density-dependent dispersal [29] including non-linear exclusion process with cell-to-cell adhesion [21, 23].

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